Zinc regulates hepatic insulin clearance  p. 6

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The LSU Health Sciences Center in Shreveport, LA is seeking candidates for the role of Vice Chancellor for Research. The individual selected for this position will provide executive leadership for research administration and planning, and will work with fellow leaders to strengthen the campus research enterprise and infrastructure for an innovative and multi-disciplinary research program across North Louisiana.

The Vice Chancellor for Research will lead the institution in all areas of research. The Vice Chancellor will represent the campus in matters related to research including federal and state agencies, other research institutions and the local community. A priority for the incumbent will be to facilitate translational research opportunities. Additionally, the Vice Chancellor will be the designated Institutional Official responsible for research across the organization.

The institution’s 436 bed University Hospital serves an urban and rural population of approximately 2.5 million, encompassing 25,000 square miles in Louisiana, East Texas, and Southwestern Arkansas. The resources for basic and clinical research are excellent.

Successful candidates must be an MD/PhD or MD with an outstanding record of scholarly achievement, including a history of independent federal research funding, serving as a principal investigator and having administrative experience relevant to clinical and basic research. Requirements include an understanding of the diverse forms of research and scholarship conducted at a comprehensive research university, and an informed perspective about federally sponsored programs, intellectual property, technology transfer and commercialization in the university setting.

The search is being led by Glenn Mills, MD, FACP, Professor of Medicine, Chief, Section of Hematology and Oncology and Director, Feist-Weiller Cancer Center. Interested candidates may submit curriculum vitae via email at ShvFacultyRecruiting@lsuhsc.edu.

Materials that cannot be submitted electronically may be mailed to: Vice Chancellor for Research Recruitment, Human Resource Management, 1501 Kings Highway, Shreveport, LA 71103.
Marc G. Caron, Ph.D., Associate Editor, is a James B. Duke Professor in the Departments of Cell Biology and Neurobiology at Duke University School of Medicine. His laboratory is interested in understanding the fundamental mechanisms that underlie the actions of neurotransmitters and GPCRs. His research uses a combination of genetics, molecular biology, cell physiology, and behavioral analysis to uncover how GPCRs are regulated and transmit signals in the brain as well as several other organs of the body. In addition, his lab is focused on understanding the role of neurotransmitters, such as dopamine, norepinephrine, and serotonin, in cellular communication within the brain and how these neurotransmitters are aberrantly regulated in disorders such as schizophrenia, depression, and Parkinson’s disease. Ongoing efforts in the laboratory examine how antipsychotics might exert their action by modulating different GPCR signaling modes and the effect of chronic antidepressants in mice with defects in serotonin synthesis. This month, Dr. Caron will be awarded the Lieber Prize for Schizophrenia Research from the Brain and Behavior Research Foundation (formerly the National Alliance for Research on Schizophrenia and Depression).

**Publication highlights**


Cardiovascular biology

**Blood pressure homeostasis is maintained by a P311–TGF-β axis**
Kameswara Rao Badri, Ming Yue, Oscar A. Carretero, Sree Latha Aramgam, Jun Cao, Stephen Sharkady, Gene H. Kim, Gregory A. Taylor, Kenneth L. Byron, and Lucia Schuger  
[http://jci.me/69884](http://jci.me/69884)

**Integrins protect cardiomyocytes from ischemia/reperfusion injury**
[http://jci.me/64216](http://jci.me/64216)

Cell biology

**p16INK4a protects against dysfunctional telomere–induced ATR-dependent DNA damage responses**
Yang Wang, Norman Sharpless, and Sandy Chang  
[http://jci.me/69574](http://jci.me/69574)

**Disruption of CEP290 microtubule/membrane-binding domains causes retinal degeneration**
Theodore G. Drivas, Erika L.F. Holzbaur, and Jean Bennett  
[http://jci.me/69448](http://jci.me/69448)

Immunology

**Human antibodies that neutralize respiratory droplet transmissible H5N1 influenza viruses**
[http://jci.me/69377](http://jci.me/69377)

**Dendritic epidermal T cells regulate skin antimicrobial barrier function**
Amanda S. MacLeod, Saskia Hemmers, Olivia Garijo, Marianne Chabod, Kerri Mowen, Deborah A. Witherden, and Wendy L. Havran  
[http://jci.me/70064](http://jci.me/70064)

**Myeloid-derived suppressor cell development is regulated by a STAT/IRF-8 axis**
Jeremy D. Waight, Colleen Netherby, Mary L. Hensen, Austin Miller, Qiang Hu, Song Liu, Paul N. Bogner, Matthew R. Farren, Kelvin P. Lee, Kebin Liu, and Scott I. Abrams  
[http://jci.me/68189](http://jci.me/68189)
Common genetic variation at the *IL1RL1* locus regulates IL-33/ST2 signaling

CVID-associated TACI mutations affect autoreactive B cell selection and activation
Neil Romberg, Nicolas Chamberlain, David Saadoun, Maurizio Gentile, Tuure Kinnunen, Yen Shing Ng, Manmeet Virdee, Laurence Menard, Tineke Cantaert, Henner Morbach, Rima Rachid, Natalia Martinez-Pomar, Nuria Matamoros, Raif Geha, Bodo Grimbacher, Andrea Cerutti, Charlotte Cunningham-Rundles, and Eric Meffre  http://jci.me/69854

With related Commentary by Antonio La Cava

Metabolism

The diabetes-susceptible gene *SLC30A8/Znt8* regulates hepatic insulin clearance

With related Commentary by Thomas V. O’Halloran, Melkam Kebede, Steven J. Philips, and Alan D. Attie

2-Aminoadipic acid is a biomarker for diabetes risk

Lipotoxicity disrupts incretin-regulated human β cell connectivity
David J. Hodson, Ryan K. Mitchell, Elisa A. Bellomo, Gao Sun, Laurent Vinet, Paolo Meda, Daliang Li, Wen-Hong Li, Marco Bugliani, Piero Marchetti, Domenico Bosco, Lorenzo Piemonti, Paul Johnson, Stephen J. Hughes, and Guy A. Rutter  http://jci.me/68459

Glucagon regulates gluconeogenesis through KAT2B- and WDR5-mediated epigenetic effects
Kim Ravnskjaer, Meghan F. Hogan, Denise Lackey, Laszlo Tora, Sharon Y.R. Dent, Jerrold Olefsky, and Marc Montminy  http://jci.me/69035

With related Commentary by Thomas R. Kleyman, Lisa M. Satlin, and Kenneth R. Hallows

Muscle biology

*ACTN3* genotype influences muscle performance through the regulation of calcineurin signaling

Nephrology

Renal β-intercalated cells maintain body fluid and electrolyte balance
Victor Gueutin, Marion Vallet, Maximilien Jayat, Janos Peti-Peterdi, Nicolas Cornière, Françoise Leviel, Fabien Sohet, Carsten A. Wagner, Dominique Eladari, and Régine Chambrey  http://jci.me/63492

With related Commentary by Thomas R. Kleyman, Lisa M. Satlin, and Kenneth R. Hallows
Research articles in the current issue of the JCI

Nephrology

Exclusive CX3CR1 dependence of kidney DCs impacts glomerulonephritis progression
http://jci.me/70143

Proximal tubule H-ferritin mediates iron trafficking in acute kidney injury
Abolfazl Zarjou, Subhashini Bolisetty, Reny Joseph, Amie Traylor, Eugene O. Apostolov, Paolo Arosio, Jozsef Balla, Jill Verlander, Deepak Darshan, Lukas C. Kuhn, and Anupam Agarwal
http://jci.me/67867

Neurobiology

A spastic paraplegia mouse model reveals REEP1-dependent ER shaping
http://jci.me/65665

With related Commentary by Ariel Y. Deutch, Peter Hedera, and Roger J. Colbran

Amelioration of ischemic brain damage by peritoneal dialysis
María del Carmen Godino, Víctor G. Romera, José Antonio Sánchez-Tomero, Jesús Pacheco, Santiago Canals, Juan Lerma, José Vivancos, María Angelese More, Magdalena Torres, Ignacio Lizasoain, and José Sánchez-Priet
http://jci.me/67284

Accelerated neurodegeneration through chaperone-mediated oligomerization of tau
Laura J. Blair, Bryce A. Nordhues, Shannon E. Hill, K. Matthew Scaglione, John C. O’Leary III, Sarah N. Fontaine, Leonid Breydo, Bo Zhang, Pengfei Li, Li Wang, Carl Cotman, Henry L. Paulson, Martin Muschol, Vladimir N. Uversky, Torsten Klengel, Elisabeth B. Binder, Rakez Kayed, Todd E. Golde, Nicole Berchtold, and Chad A. Dickey
http://jci.me/69003

Oncology

Epithelial stem cell mutations that promote squamous cell carcinoma metastasis
Ruth A. White, Jill M. Neiman, Anand Reddi, Gangwen Han, Stanca Birlea, Doyel Mitra, Laikuan Dionne, Pam Fernandez, Kazutoshi Murao, Li Bian, Stephen B. Keysar, Nathaniel B. Goldstein, Ningjing Song, Sophia Bornstein, Zheyi Han, Xian Lu, Joshua Wisell, Fulin Li, John Song, Shi-Long Lu, Antonio Jimeno, Dennis R. Roop, and Xiao-Jing Wang
http://jci.me/65856

Radiation-induced acid ceramidase confers prostate cancer resistance and tumor relapse
http://jci.me/64791

Thrombospondin-1 mediates oncogenic Ras–induced senescence in premalignant lung tumors
Kwan-Hyuck Baek, Dongha Bhang, Alexander Zaslavsky, Liang-Chuan Wang, Anil Vachani, Carla F. Kim, Steven M. Alibelda, Gerard I. Evan, and Sandra Ryeom
http://jci.me/67465

ErbB3 downregulation enhances luminal breast tumor response to antiestrogens
Meghan M. Morrison, Katherine Hutchinson, Michelle M. Williams, Jamie C. Stanford, Justin M. Balko, Christian Young, Maria G. Kuba, Violeta Sánchez, Andrew J. Williams, Donna J. Hicks, Carlos L. Arteaga, Aleix Prat, Charles M. Perou, H. Shelton Earp, Suleiman Massarweh, and Rebecca S. Cook
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Perturbation of NK cell peripheral homeostasis accelerates prostate carcinoma metastasis  
Gang Liu, Shengjun Lu, Xuanjun Wang, Stephanie T. Page, Celestia S. Higano, Stephen R. Plymate, Norman M. Greenberg, Shaoli Sun, Zihai Li, and Jennifer D. Wu  
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Pak and Rac GTPases promote oncogenic KIT–induced neoplasms  
Holly Martin, Raghvveer Singh Mali, Peilin Ma, Anindya Chatterjee, Baskar Ramdas, Emily Sims, Veerendra Munugalavadla, Joydeep Ghosh, Ray R. Mattingly, Valeria Visconte, Ramon V. Tiu, Cornelis P. Vlaar, Suragani Dharmawardhane, and Reuben Kapur  
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PP2A-activating drugs selectively eradicate TKI-resistant chronic myeloid leukemia stem cells  
http://jci.me/68951

FGF18 as a prognostic and therapeutic biomarker in ovarian cancer  
Wei Wei, Samuel C. Mok, Esther Oliva, Sung-hoon Kim, Gayatry Mohapatra, and Michael J. Birrer  
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A SALL4/MLL/HOXA9 pathway in murine and human myeloid leukemogenesis  
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Inhibiting glycolytic metabolism enhances CD8+ T cell memory and antitumor function  
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Maternal uterine NK cell–activating receptor KIR2DS1 enhances placentation  
Shiqiu Xiong, Andrew M. Sharkey, Philippa R. Kennedy, Lucy Gardner, Lydia E. Farrell, Olympe Chazara, Julien Bauer, Susan E. Hiby, Francesco Colucci, and Ashley Moffett  
http://jci.me/68991

Retinal angiogenesis suppression through small molecule activation of p53  
Sai H. Chavala, Younghee Kim, Laura Tdusco, Valerie Catiello, Till Milde, Nagaraj Kerur, Nidia Claros, Susan Yanni, Victor H. Guaiquil, William W. Hauswirth, John S. Penn, Shahin Rafii, Sandro De Falco, Thomas C. Lee, and Jayakrishna Ambati  
http://jci.me/67315

Vascular biology

Kruppel-like factor 15 is critical for vascular inflammation  
http://jci.me/68552

Retinal angiogenesis suppression through small molecule activation of p53  
Sai H. Chavala, Younghee Kim, Laura Tdusco, Valerie Catiello, Till Milde, Nagaraj Kerur, Nidia Claros, Susan Yanni, Victor H. Guaiquil, William W. Hauswirth, John S. Penn, Shahin Rafii, Sandro De Falco, Thomas C. Lee, and Jayakrishna Ambati  
http://jci.me/67315
When insulin is secreted from β cells, it first flows to the liver via the portal vein. Some insulin enters the liver and is subsequently cleared, while the remaining insulin enters the systemic circulation to target peripheral tissues. In this issue, Motoyuki Tamaki, Yoshio Fujitani, and colleagues uncover a surprising role for zinc in regulating the rate of insulin clearance in liver. The SLC30A8 gene, which encodes a zinc transporter, has several common variants that are associated with increased susceptibility to type 2 diabetes; however, it has been unclear how alterations in these variants contribute to the disease. Using conditional knockout mice that lack Slc30a8 expression in pancreatic β cells, the research team found that mutant mice had enhanced insulin secretion, but paradoxically low peripheral insulin levels. Similarly, humans with a risk allele of SLC30A8 also exhibited increased insulin clearance. Loss of Slc30a8 resulted in elevated clathrin-mediated endocytosis and degradation of insulin during its first pass through the liver. Furthermore, exogenously delivered zinc suppressed hepatic insulin clearance by preventing clathrin-mediated endocytosis in the liver. This study sheds light on the role of zinc in insulin granules in the pancreas and why variants in SLC30A8 lead to increased risk of developing type 2 diabetes. The image shows a false-colored electron micrograph of a murine pancreas that is mosaic for Slc30a8 expression, with dense insulin granules in normal tissue (blue) and low-density insulin granules in mutant tissue (purple). In the accompanying Commentary, Alan Attie and colleagues discuss how hepatic insulin clearance could serve as a new therapeutic target in the treatment of diabetes.
New insights into ciliopathy-associated mutations

Centrosomal protein 290 kDa (CEP290) plays a critical role in ciliogenesis, and mutations in CEP290 have been linked to a variety of human ciliopathies that cause disorders of the eyes, brain, and kidneys; however, it is unclear how the disease-linked mutations alter the function of the protein. In this issue, Theodore Drivas and colleagues identified four functional domains within the protein, including two autoinhibitory domains, an amphipathic helix motif that regulates membrane binding, and a microtubule-binding domain. Importantly, disruption of the microtubule-binding domain, the site of many human mutations, markedly reduced ciliogenesis, leading to retinal degeneration. Taken together, these findings provide new insight into the function of CEP290 and its role in the pathogenesis of ciliopathies.

Disruption of CEP290 microtubule/membrane-binding domains causes retinal degeneration
Theodore G. Drivas, Erika L.F. Holzbaur, and Jean Bennett
http://jci.me/69448

Glucose homeostasis regulator is a biomarker for diabetes risk

Type 2 diabetes mellitus affects an estimated 366 million people worldwide, making the identification of those at risk for the disease a public health priority. Thomas Wang and colleagues developed a platform to measure 70 different intermediary metabolites in 188 individuals who developed diabetes and 188 propensity-matched controls from participants who were followed for 12 years as part of the Framingham Heart Study. They found that 2-aminoadipic acid (2-AAA) levels had the strongest association with future diabetes. In mice, administration of 2-AAA lowered fasting plasma glucose levels regardless of diet. Moreover, 2-AAA enhanced insulin secretion in both human and mouse pancreatic β cells. These findings suggest that plasma measurements of 2-AAA could help identify candidates for interventions to help prevent type 2 diabetes.

2-Aminoadipic acid is a biomarker for diabetes risk
http://jci.me/64801

Type I distal renal tubular acidosis (dRTA) is characterized by abnormal acid-base balance in the kidneys. Patients with an inherited form of dRTA have inactivating mutations in ATP6V1B1 or ATP6V0A4, which encode subunits of an apical vacuolar proton pump, or in SLC4A1, which encodes a basolateral Cl−/HCO3− exchanger in the α-intercalated cells (α-ICs) of the nephron. In addition to abnormal acid-base balance, these patients exhibit salt- and potassium-losing nephropathy and mineral imbalances that ultimately lead to chronic kidney failure; however, the mineral imbalances do not appear to be linked to α-IC dysfunction. Victor Gueutin and colleagues report that dRTA-associated salt- and potassium-losing nephropathy is a consequence of proton pump defects in β-intercalated cells (β-ICs). Using mice with Atpt6v1b1 disruption, they demonstrated that impairment of the proton pump in the β-ICs activates a paracrine ATP/prostaglandin E2 signaling cascade (see accompanying image) that impairs the function of neighboring principal cells (PCs), which mediate electrolyte and water balance. In the accompanying Commentary, Thomas Kleyman and colleagues discuss the implications of crosstalk among cells in the distal nephron.

Renal β-intercalated cells maintain body fluid and electrolyte balance
Victor Gueutin, Marion Vallet, Maximilen Jayat, Janos Peti-Peterdi, Nicolas Comière, Françoise Leviel, Fabien Sohet, Carsten A. Wagner, Dominique Eladari, and Régine Chambrey
http://jci.me/63492

Related Commentary
Opening lines of communication in the distal nephron
Thomas R. Kleyman, Lisa M. Satlin, and Kenneth R. Hallows
http://jci.me/71944

A balancing act in the kidneys

Type I distal renal tubular acidosis (dRTA) is characterized by abnormal acid-base balance in the kidneys. Patients with an inherited form of dRTA have inactivating mutations in ATP6V1B1 or ATP6V0A4, which encode subunits of an apical vacuolar proton pump, or in SLC4A1, which encodes a basolateral Cl−/HCO3− exchanger in the α-intercalated cells (α-ICs) of the nephron. In addition to abnormal acid-base balance, these patients exhibit salt- and potassium-losing nephropathy and mineral imbalances that ultimately lead to chronic kidney failure; however, the mineral imbalances do not appear to be linked to α-IC dysfunction. Victor Gueutin and colleagues report that dRTA-associated salt- and potassium-losing nephropathy is a consequence of proton pump defects in β-intercalated cells (β-ICs). Using mice with Atpt6v1b1 disruption, they demonstrated that impairment of the proton pump in the β-ICs activates a paracrine ATP/prostaglandin E2 signaling cascade (see accompanying image) that impairs the function of neighboring principal cells (PCs), which mediate electrolyte and water balance. In the accompanying Commentary, Thomas Kleyman and colleagues discuss the implications of crosstalk among cells in the distal nephron.

Renal β-intercalated cells maintain body fluid and electrolyte balance
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http://jci.me/63492

Related Commentary
Opening lines of communication in the distal nephron
Thomas R. Kleyman, Lisa M. Satlin, and Kenneth R. Hallows
http://jci.me/71944
Peritoneal dialysis reduces the post-stroke glutamate spike

**Ischemic stroke** is one of the leading causes of death and disability. It is associated with elevated blood levels of L-glutamate, an excitatory neurotransmitter that triggers cell death. María C. Godino and colleagues developed a method based on peritoneal dialysis to reduce blood glutamate levels and accelerate brain glutamate clearance. Using a rat model of stroke, they found that the procedure reduced the stroke-associated glutamate increase and resulted in a smaller infarct area. The accompanying image shows functional magnetic resonance imaging of cerebral cortex function in a normal animal, a rat that has suffered from a stroke, and a rat treated with peritoneal dialysis.

Additionally, Godino and colleagues found that patients undergoing peritoneal dialysis for kidney failure had lower blood glutamate levels, indicating that this treatment can reduce glutamate in humans as well as rats. These findings suggest that peritoneal dialysis could potentially reduce stroke damage in humans.

**A spastic paraplegia mouse model reveals REEP1-dependent ER shaping**


**Related Commentary**

REEPing the benefits of an animal model of hereditary spastic paraplegia

Ariel Y. Deutch, Peter Hedera, and Roger J. Colbran [http://jci.me/72324](http://jci.me/72324)
Dose-dependent effect of TACI mutations on common variable immune deficiency

Multiple heterozygous mutations in tumor necrosis factor receptor superfamily member 13B (TACI) are associated with common variable immune deficiency (CVID), a group of diseases characterized by antibody deficiency, susceptibility to infection, and autoimmunity. In this issue, Neil Romberg and colleagues assessed how the number of TACI mutations affects B cell function. They found that TACI mutations impair the removal of autoreactive B cells at the central B cell tolerance checkpoint in all carriers, regardless of the number of mutations, but that healthy individuals mitigated this defect with an effective peripheral B cell tolerance checkpoint. Additionally, a single TACI mutation was correlated with the presence of circulating T follicular helper (Tfh) cells and a high incidence of autoimmunity, while two mutations correlated with a lack of circulating Tfh cells and a lack of autoimmune complications. This study clarifies the role of TACI mutations in B cell function and CVID.

In the accompanying Commentary, Antonio La Cava speculates on how these findings could benefit CVID patients.

CVID-associated TACI mutations affect autoreactive B cell selection and activation
Neil Romberg, Nicolas Chamberlain, David Saadoun, Maurizio Gentile, Tuure Kinnunen, Yen Shing Ng, Mammeet Virdee, Laurence Menard, Tineke Cantatore, Henner Morbach, Rima Rachid, Natalia Martinez-Pomar, Nuria Matamoros, Raif Geha, Bodo Grimbacher, Andrea Cerutti, Charlotte Cunningham-Rundles, and Eric Meffre
http://jci.me/69854

Related Commentary
Common variable immunodeficiency: two mutations are better than one
Antonio La Cava  http://jci.me/72476

Defending the skin after injury

The outer layer of the skin forms a barrier that protects the rest of the body from environmental and pathogenic insult. In addition to serving as a physical barrier, the skin also contains antimicrobial peptides and proteins (AMPs) that help defend against pathogens and participate in wound healing. When this barrier is breached by injury, such as a cut, this protective effect is severely compromised. Repair is mediated by dendritic epidermal T cells (DETCs), which recognize damaged keratinocytes in a TCR-dependent manner. In this issue, Amanda MacLeod and colleagues demonstrate that TCR stimulation induces secretion of AMPs and proteins that regulate keratinocyte migration, proliferation, and differentiation, establishing a role for IL-17A–secreting DETCs in barrier function and wound healing.

Dendritic epidermal T cells regulate skin antimicrobial barrier function
Amanda S. MacLeod, Saskia Hemmers, Olivia Garijo, Marianne Chabod, Keni Mowen, Deborah A. Witherden, and Wendy L. Havran  http://jci.me/70064

Driving myeloid-derived suppressor cell development

Myeloid-derived suppressor cells (MDSCs), which inhibit innate and adaptive immune responses, have emerged as a significant barrier to the use of cancer immunotherapies; however, the MDSC developmental program is incompletely understood. In this issue, Scott Abrams and colleagues identified interferon regulatory factor-8 (IRF-8) as an integral component of the transcriptional program that controls MDSC subset development. Irf8-deficient mice had myeloid populations that were highly similar to tumor-induced MDSCs, while rescue of IRF-8 reduced MDSC accumulation and increased immunotherapeutic efficacy in a murine model of mammary cancer. Decreases in IRF-8 expression were initiated by the tumor-derived MDSC-inducing factors G-CSF and GM-CSF, via STAT3- and STAT5-dependent signaling pathways. Moreover, decreased IRF-8 levels in breast cancer patients were correlated with increased frequencies of MDSCs compared with those in healthy controls and were associated with a poorer prognosis. These findings advance the notion that immunotherapeutic efficacy is improved when combined with anti-MDSC tactics that target developmental and functional elements of MDSC biology.

Myeloid-derived suppressor cell development is regulated by a STAT/IRF-8 axis
Jeremy D. Waight, Colleen Netherby, Mary L. Hensen, Austin Miller, Qiang Hu, Song Liu, Paul N. Bogner, Matthew R. Farren, Kelvin P. Lee, Kebin Liu, and Scott I. Abrams
http://jci.me/68189
**Research | Editor’s Picks**

### Oncology

**Radiation therapy** has increasingly become the treatment of choice for patients with prostate cancer who have not yet undergone prostatectomy. Unfortunately, subpopulations of prostate cancer cells escape from radiation-induced killing, leading to relapse. In this issue, Joseph Cheng and colleagues demonstrate that radiation induces activation of the gene encoding the ceramide-metabolizing enzyme, acid ceramidase (ASAH1/AC), which leads to production of prosurvival sphingolipids. Overexpression of AC in prostate cancer clones that had survived radiotherapy was associated with increased proliferation and resistance to radiation. Further, human prostate cancer tissues exhibited higher levels of AC after radiotherapy failure compared with untreated tumors, premalignant tissue, or benign tissue. The accompanying image shows enhanced AC expression in radiotherapy-treated compared with untreated prostate cancer. In a xenograft model, treatment with both an AC inhibitor and radiotherapy produced a durable cure in mice, indicating that AC inhibitors could serve as an adjuvant for radiotherapy in prostate cancer.

**Radiation-induced acid ceramidase confers prostate cancer resistance and tumor relapse**


[http://jci.me/64791](http://jci.me/64791)

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**Differential effects of soluble and membrane-bound NK-activating ligands**

**NK cell group 2 member D (NKG2D)** is an activating receptor expressed by NK and CD8+ T cells. Induction of NKG2D ligands on tumor cells in response to genotoxic stress sensitizes tumor cells to NK- and sometimes T cell–mediated lysis. Surprisingly, many human tumors abundantly express NKG2D ligands and still progress to advanced disease. To understand the impact of NKG2D ligands on cancer progression, Gang Liu and colleagues engineered two humanized bitransgenic mouse models of prostate cancer that express the native human NKG2D ligand MHC class I polypeptide-related sequence B (MICB) or a membrane-restricted form of the ligand. They found that, similar to prostate cancer patients, mice expressing MICB had accelerated cancer progression, which was associated with elevated serum levels of soluble MICB and loss of peripheral NK cells. Conversely, mice expressing membrane-restricted MICB exhibited long-term, tumor-free survival. These findings shed light on the differential impact of alternative forms of NKG2D ligands on tumor immunity.

**Perturbation of NK cell peripheral homeostasis accelerates prostate carcinoma metastasis**

Gang Liu, Shengjun Lu, Xuanjun Wang, Stephanie T. Page, Celestia S. Higano, Stephen R. Plymate, Norman M. Greenberg, Shaoji Sun, Zihai Li, and Jennifer D. Wu

[http://jci.me/69369](http://jci.me/69369)

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**Cellular metabolic switch alters CD8+ T cell antitumor activity**

CD8+ T cells mediate the adaptive immune response to intracellular pathogens and cancer. Upon encountering an antigen, T cells shift from using fatty acid oxidation to glycolysis as the primary metabolic mode. To determine whether this metabolic shift influences the ability of T cells to become long-lived memory cells, Madhusudhanan Sukumar and colleagues used a fluorescent glucose analog to quantify glucose uptake in activated CD8+ T cells. They found that cells that took up limited amounts of glucose (i.e., were not primarily reliant on glycolysis) were more likely to become long-lived memory cells. Enforced reliance on glycolytic metabolism severely impaired the formation of long-lived memory T cells, whereas pharmacological inhibition of this metabolic pathway enhanced memory T cell formation and antitumor function. These results indicate that alterations in cellular metabolism could significantly influence the effectiveness of T cell–based therapeutics.

**Inhibiting glycolytic metabolism enhances CD8+ T cell memory and antitumor function**


[http://jci.me/69589](http://jci.me/69589)
**CARDIOVASCULAR BIOLOGY**

Getting a grip in cardiac ischemia/reperfusion injury

Integrins are transmembrane receptors that anchor cells to the ECM. Additionally, they transduce adhesive and mechanical signals that directly initiate intracellular signaling events. After ischemia/reperfusion (I/R) injury, such as myocardial infarction (MI), cardiomyocyte β1D integrin is downregulated, indicating that it may play a role in decreased function after MI. In this issue, Hideshi Okada and colleagues demonstrate that integrins protect cardiomyocytes after I/R injury. As seen in the accompanying image, cardiac-specific loss of β1D integrin enhanced damage after I/R. Using isolated cardiomyocytes, Okada and colleagues found that integrins stabilized the ryanodine receptor RyR2, which mediates calcium supplies in cardiac muscle. Based on these findings, Okada and colleagues propose that this interaction modifies cardiac calcium pathways to protect the myocardium.

Integrins protect cardiomyocytes from ischemia/reperfusion injury


http://jci.me/64216

**REPRODUCTIVE BIOLOGY**

A critical combination in trophoblast/maternal decidual NK cells

Invasion of the uterine decidua by fetal extravillous trophoblast (EVT) instigates vascular remodeling of the uterine arteries, which is required to provide an adequate blood supply to the growing fetus. Both reduced invasion and overinvasion by EVT have been linked to pregnancy complications such as recurrent miscarriage, fetal growth restriction, preeclampsia, and uterine rupture. During invasion, trophoblasts encounter decidual NK cells (dNK). Genetic studies have indicated that particular combinations of dNK-expressed killer cell immunoglobulin-like receptors (KIR2DL1 and KIR2DS1) and HLA-C group 2 alleles (HLA-C2) expressed by EVT contribute to pregnancy disorders. In this issue, Shiqiu Xiong and colleagues examined how these different maternal/fetal genetic combinations affect placentation and used microarrays to identify cellular responses triggered by the binding of KIRs to HLA-C2. Importantly, they found that KIR2DS1 activation stimulated the production of GM-CSF and enhanced EVT migration in vitro (see the accompanying image). These findings provide insight into how the interaction of the maternal activating NK receptor KIR2DS1 with trophoblast HLA-C influences placentation.

KIRs to HLA-C2. Importantly, they found that KIR2DS1 activation stimulated the production of GM-CSF and enhanced EVT migration in vitro (see the accompanying image). These findings provide insight into how the interaction of the maternal activating NK receptor KIR2DS1 with trophoblast HLA-C influences placentation.

Maternal uterine NK cell–activating receptor KIR2DS1 enhances placentation

Shiqiu Xiong, Andrew M. Sharkey, Philippa R. Kennedy, Lucy Gardner, Lydia E. Farrell, Olympe Chazara, Julien Bauer, Susan E. Hiby, Francesco Colucci, and Ashley Moffett

http://jci.me/68991
The MDM2 inhibitor Nutlin-3 reduces retinal angiogenesis

Age-related macular degeneration is caused by pathological angiogenesis within the retina. New therapeutic strategies have focused on neutralization of the proangiogenic cytokine VEGF; however, responses to anti-VEGF therapy are not durable. Murine double minute-2 (MDM2) inhibitors have the potential advantage of directly targeting abnormal blood vessels through activation of the tumor suppressor p53. Sai Chavala and colleagues investigated the antiangiogenic activity of the MDM2 inhibitor Nutlin-3, which activates p53 by preventing its ubiquitin-mediated degradation. Using a murine model of retinal vascular development, Chavala and colleagues found that Nutlin-3 reduced retinal vascular growth in postnatal eyes (see accompanying image of control [top] and Nutlin-3–treated [bottom] retina). These results suggest that MDM2 inhibitors could potentially be used to treat pathological angiogenesis.

The MDM2 inhibitor Nutlin-3 suppresses retinal angiogenesis through small molecule activation of p53

Sai H. Chavala, Younghee Kim, Laura Tudisco, Valeria Cicatiello, Till Milde, Nagaraj Kerur, Nidia Claros, Susan Yanni, Victor H. Guaiquil, William W. Hauswirth, John S. Penn, Shahin Rafii, Sandra De Falco, Thomas C. Lee, and Jayakrishna Ambati

http://jci.me/67315

Kruppel-like factor 15 protects against vascular inflammation

Proinflammatory activation of vascular smooth muscle cells (VSMCs), which are the dominant constituent of the vessel wall, is a major contributor to vascular disease; however, the factors that regulate this activation are incompletely defined. Yuan Lu and colleagues examined the role of Kruppel-like factor 15 (KLF15), a member of a family of transcription factors that regulate the inflammatory response, in vascular disease. They found that KLF15 levels were markedly reduced in human atherosclerotic tissues and that VSMC-specific loss of KLF15 promoted vascular inflammation in two different murine models of vascular disease. Lu and colleagues further demonstrated that KLF15 interacts with the histone acetyltransferase p300 to decrease acetylation/activation of the proinflammatory factor NF-κB. These findings demonstrate that KLF15 is an essential regulator of vascular inflammation, suggesting that it may be a suitable therapeutic target in vascular disease.

Kruppel-like factor 15 is critical for vascular inflammation


http://jci.me/68552
Identification of a mammalian drug transporter

Mammalian \textit{P}-glycoproteins are ATP-dependent drug transport proteins that impede the entry of therapeutic compounds into a variety of tissues, particularly the blood-brain barrier and the gut. In 1994, Alfred Schinkel and Piet Borst published an article in the \textit{JCI} reporting the effects of \textit{P}-glycoprotein deficiency in mice. Absence of functional \textit{P}-glycoprotein in mice resulted in highly increased brain penetration of a number of drugs and, in some cases, resulted in severe neurotoxicity or fundamentally altered pharmacological effects. In this issue, Borst and Schinkel reflect on their initial findings, discussing the generation of knockout mice in the early 1990s and the impact of this discovery on pharmacology.

\textbf{P-glycoprotein ABCB1: a major player in drug handling by mammals}

Piet Borst and Alfred H. Schinkel  \url{http://jci.me/70430}

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New therapeutic modalities in gastrointestinal motility disorders

\textit{Gastrointestinal motility disorders}, including irritable bowel syndrome, gastroparesis, chronic diarrhea, constipation, and visceral pain, account for nearly half of all gastroenterology referrals and represent a substantial disease burden. Both basic and translational research have made substantial contributions to our understanding of these diseases and have resulted in the development of new therapeutic modalities for their treatment. In this issue, Michael Camilleri discusses the pathology that underlies motility disorders and reviews recent and ongoing clinical trials of new medications for the treatment of esophageal sensorimotor disorders, gastroparesis, visceral pain, chronic constipation, and chronic diarrhea.

\textbf{Pharmacological agents currently in clinical trials for disorders in neurogastroenterology}

Michael Camilleri  \url{http://jci.me/70837}

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Immune responses to hepatitis C infection

\textbf{The hepatitis C virus (HCV)} is a single-stranded RNA virus that primarily affects the liver in infected individuals. Nearly 180 million people are infected globally, and complications stemming from chronic HCV infection are a major cause of cirrhosis and liver cancer. While recent years have witnessed the development of important antiviral therapies, a proportion of patients fail to exhibit a sustained antiviral response, and a vaccine has yet to be developed. In his review, Hugo Rosen explores the complex interplay between adaptive and innate immune cells elicited by HCV infection as well as the underlying molecular pathways that are important in determining the response to anti-HCV therapy. In addition, Rosen touches on genome-wide association studies that suggest mechanisms by which some individuals can spontaneously clear infection.

\textbf{Emerging concepts in immunity to hepatitis C virus infection}

Hugo R. Rosen  \url{http://jci.me/67714}

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Aaron Ciechanover

\textbf{The regulated degradation of cellular proteins} is critical to the function of cells. After the discovery of the lysosome in 1949, it was assumed that proteins were degraded within this organelle; however, several lines of evidence indicated that an energy-dependent, non-lysosomal process mediated intracellular protein degradation. The process turned out to be mediated by the ubiquitin-proteasome system (UPS), which is involved in a broad array of cellular processes, including cell division, cell cycle progression, and protein quality control. This month \textit{JCI} Editor at Large Ushma Neill interviews Aaron Ciechanover, who shared the 2004 Nobel Prize in Chemistry with Avram Hershko and Irwin Rose for the discovery of the UPS.

\url{http://jci.me/71859}

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Hindsight

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2013 LASKER AWARDS

The JCI is pleased to partner with the Lasker Foundation to present profiles on the Foundation’s 2013 award winners. Read the JCI’s coverage, now freely available online.

Richard Scheller and Thomas Südhof receive the 2013 Albert Lasker Basic Medical Research Award
Jillian H. Hurst
http://jci.me/72681

Hearing restoration: Graeme Clark, Ingeborg Hochmair, and Blake Wilson receive the 2013 Lasker–DeBakey Clinical Medical Research Award
Corinne Williams
http://jci.me/72707

Bill and Melinda Gates honored with Lasker–Bloomberg Public Service Award
Sarah Jackson
http://jci.me/72874